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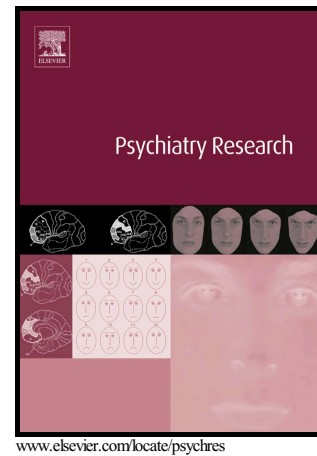
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The prevalence of diabetes mellitus type 2 in people with alcohol use disorders: a systematic review and large scale meta-analysis

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The prevalence of diabetes mellitus type 2 in people with alcohol use disorders: a systematic review and large scale meta-analysis

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Abstract

Type 2 Diabetes Mellitus (T2DM) is highly predictive of cardiovascular diseases and is associated with worse quality of life and increased healthcare utilisation. The current meta-analysis aimed to (i) describe the pooled prevalence of T2DM in people with alcohol use disorders (AUDs), (ii) investigate the impact of demographic, clinical and treatment factors, and (iii) compare T2DM prevalences in AUDs versus the general population. The trim and fill adjusted pooled T2DM prevalence among 3,998 people with AUDs (age range 34.8 to 51.1 years; 76.6% male) (N studies=7) was 12.4% (95%CI=11.8%-13.9%). Higher T2DM prevalences were observed in studies with a higher mean age and a higher percentage of male participants, and in studies with self- or physician reported T2DM assessment. A trend for higher T2DM prevalences was found in inpatient settings, in studies assessing T2DM with the gold-standard oral glucose tolerance test compared with fasting glucose only, and with studies including patients with a higher percentage of physical co-morbidity. Although healthy control data are lacking, the pooled prevalence is similar to that observed in people with

severe mental illness who are considered a high-risk group. Routine screening and multidisciplinary management of T2DM in people with AUDs is needed.

Introduction

In general population surveys people with alcohol use disorders (AUDs) experience an excess mortality rate two times higher than those without AUDs (Roerecke and Rehm, 2013). Compared with the general population, people with AUD have more than a 10-fold risk of mortality from liver cirrhosis, a seven-fold risk for injury fatalities and a two-fold risk for cardiovascular and cancer deaths (Roerecke and Rehm, 2014).

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases. It confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes (Collaboration, 2010). Major risk factors for T2DM in people with AUDs include the high risk for acute pancreatitis (Das et al., 2013), unhealthy lifestyle behaviors such as lack of sufficient physical activity (Smothers and Bertolucci, 2001), co-morbid substance abuse (McKee et al., 2007) in particular smoking (Goodwin et al., 2013) and an impaired cardiorespiratory fitness (Herbsleb et al., 2013). Once developed, patients with AUDs have a severely impaired diabetes self-management and worse health outcomes (Thomas et al., 2012). Prevention and treatment of T2DM therefore demands careful consideration in clinical practice, and particularly in those with an increased risk for cardiovascular diseases and associated premature mortality (Alberti and Zimmet, 1998). Several reviews on alcoholism and T2DM indicated that chronic heavy consumption deteriorates glucose tolerance and insulin resistance, and this may well be one of the mechanisms involved in the malignant effect of alcohol, with regard to development of T2DM (Conigrave and Rimm, 2003; Howard et al., 2004; Kim and Kim, 2012; Li et al., 2016; Molina et al., 2014).

However, meta-analytic data considering the prevalence of T2DM and its moderators are currently lacking in the literature. Pooling T2DM prevalence data in people with AUDs allows for investigation of the effect of demographic variables (e.g., age, gender, illness duration), clinical (e.g., % psychiatric co-morbidity, % physical co-morbidity, % smoking) and treatment (e.g., psychotropic medication use) related factors. If risk stratification is observed, this could potentially help guide clinicians in monitoring and treating high-risk individuals. Given the aforementioned gap within the literature, we conducted a systematic review and meta-analysis of pooled T2DM prevalences in

people with AUDs. We aimed to (i) describe pooled T2DM frequencies in AUDs, (ii) analyze the influence of demographic, clinical and treatment variables as well as T2DM assessment methods, and (iii) compare T2DM prevalence in studies directly comparing people with AUD with general population samples.

Methods

This systematic review was conducted in accordance with the MOOSE guidelines (Stroup et al., 2000) and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (Moher et al., 2009).

Inclusion and exclusion criteria

Included were: (1) observational studies (cross-sectional, retrospective and prospective studies) and baseline data of randomized controlled trials; (2) studies involving adults with a standardized primary diagnosis of alcohol use disorder, alcohol dependence, harmful alcohol use, alcohol abuse as diagnosed by the DSM-IV (American Psychiatric Association, 1994), DSM 5 (American Psychiatric Association, 2013) or the International Classification of Disease (WHO, 1993) or an Alcohol Use Disorders Identification Test (AUDIT) score of ≥ 15 (i.e. likely severe alcohol problem) (Babor et al., 2001), irrespective of clinical setting (inpatient, outpatient or mixed) and, (3) studies that reported study-defined T2DM prevalences. We excluded: (1) case reports, (2) conference abstracts, and (3) studies restricted to patients with cardiometabolic diseases or excluding at risk patients. When required, we contacted the primary or corresponding authors of studies up to two times in a one-month period to (1) confirm eligibility, and (2) obtain the data required for analysis if they were not available in the published paper.

Search criteria, study selection and critical appraisal

Two independent authors (DV, BS) searched Medline, PsycARTICLES, Embase and CINAHL from database inception to March 1st, 2015 without language restrictions. Key words used were “diabetes” or “glucose” or “hyperglycemia” AND “alcohol dependence” OR “alcohol abuse” OR “alcohol misuse” OR “harmful alcohol use” OR “alcohol use disorders” in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles. After the removal of duplicates, reviewers screened the titles and abstracts of all potentially eligible articles. Both authors

applied the eligibility criteria, and a list of full text articles was developed through consensus. The two reviewers then considered the full texts of these articles and the final list of included articles was reached through consensus. A third reviewer (MDH) was available for mediation throughout this process. Methodological appraisal was performed according to PRISMA standards (Moher et al., 2009), including evaluation of bias (confounding, overlapping data, publication bias). Publication bias was tested using the Egger's regression method (Egger et al., 1997) and Begg-Mazumdar test (Begg and Mazumdar, 1994), with a p-value <0.05 suggesting the presence of bias.

Statistical analyses

We pooled individual study data using the DerSimonian-Laird proportion method with StatsDirect (DerSimonian and Laird, 1986). The trim-and-fill approach (Duval and Tweedie, 2000) was used to adjust the overall estimate for funnel plot asymmetry. Due to anticipated heterogeneity, a random effects meta-analysis was employed. Heterogeneity was measured with the Q statistic, yielding a chi-square p-value with $p < 0.05$ indicating significant heterogeneity of the pooled results. If available, we compared the prevalence of T2DM between people with AUDs and general population control groups with AUD that were matched on age and sex, only using data from studies in which they were directly compared. Furthermore, in the entire dataset, we conducted subgroup analyses to investigate gender differences, differences across settings (inpatients, outpatients or community patients, mixed), geographical regions, differences between population and non-population based studies, and between methods of T2DM assessment (fasting glucose testing, OGTT, self- or physician report, charts). Further, we conducted meta-regression analyses to investigate potential moderators [age, percentage male, illness duration, smoking (%), physical inactivity (%), employment status (% employed), marital status (% single), % psychiatric co-morbidity (DSM or ICD), % physical co-morbidity (ICD)] and treatment-factors (% on psychotropic medication) with Comprehensive Meta Analysis (version 3). The significance level was set at $P \leq 0.05$.

Results

Search results and included participants

After excluding duplicates and irrelevant hits, our search yielded 31 potential publications of which 7 (including 9 T2DM prevalences) (Chandini and Mathai, 2013; David et al., 2004; Glaus et al., 2013;

Hong et al., 2015; Ju et al., 2011; Odlaug et al., 2015; Pach et al., 2013) met the inclusion criteria (Figure 1). All included studies adopted a cross-sectional design. While in 2 studies T2DM was diagnosed according to the gold-standard oral glucose intolerance test (OGTT), 5 studies assessed T2DM following fasting glucose assessment and 2 studies relied on self- or physician reports. The final sample comprised 3,998 unique persons with AUDs but no matched controls. Sample sizes ranged from 88 to 1,660 participants with a median sample size of 173. At study level, the mean age of participants with AUD ranged from 34.8 to 51.1 years, 76.6% were male, and mean illness duration (N studies=3) was 16.2 years (range=10.6-26.6 years). More details of the included studies and participants are presented in Table 1.

Prevalence of T2DM

The estimated weighted mean prevalence of T2DM among 3,998 people with AUDs was 11.9% (95%CI= 9.3% to 15.1%; $Q=40.9$, $p<0.001$). The Begg-Mazumdar (Kendall's tau=-0.08, $p=0.75$) and Egger test (bias=-0.63; 95%CI=-0.38 to 2.62; $p=0.066$) indicated no strong evidence for the presence of publication bias. Applying the trim and fill method and adjusting for 2 studies, the prevalence of T2DM slightly increased to 12.4% (95%CI=11.8% to 13.9%).

Subgroup analyses and predictors of T2DM

The pooled prevalences across different treatment settings (inpatients, outpatients, community patients, mixed settings), and population versus non-population based), methods of T2DM assessment (fasting glucose testing, OGTT, self- or physician report, charts) are summarized in Table 1. The separate meta-regressions are presented in Table 2. There were no significant overall differences between different treatment settings although when directly comparing the pooled T2DM between inpatient (16.1%; 95%CI=9.6%-25.8%) and community settings (7.0%; 95%CI=3.4%-13.9%), a trend level of significance was observed of higher prevalence in inpatient studies ($P=0.09$). The pooled T2DM prevalence in population-based studies (9.9%; 95%CI=7.5%-12.9%) was significantly ($P=0.015$) lower than in clinical-based (non-population, 17.2%; 95%CI=12.0%-24.0%) studies. A lower T2DM prevalence was observed in studies relying upon clinical data gleaned from fasting glucose (8.5%; 95%CI=5.7%-12.4%) versus self-report studies (16.9%; 95%CI=10.2%-26.7%) ($P=0.02$). There was also a trend for a lower T2DM prevalence when using fasting glucose instead of the gold-

standard OGTT. Also pooled T2DM prevalences per geographical region are displayed in Table 1. No significant geographical differences were observed.

Separate meta-regression analyses (see Table 3 for β values and 95% CI) revealed that higher T2DM frequencies were moderated by older age (years) ($P=0.015$), a higher proportion of males (% male) ($P=0.003$), while there was a trend ($P=0.103$) for higher % physical co-morbidity.

Relative risk of T2DM in persons with AUD compared with general population controls

There were no data available comparing the T2DM prevalence of people with AUD versus age- and gender matched controls.

Discussion

General findings

To the authors' knowledge, this is the first meta-analysis of T2DM in people with AUDs. Approximately one in 8 individuals with AUDs has T2DM, i.e 12.4% (95%CI=11.8% to 13.9%). When restricting the pooled T2DM prevalence to population-based studies the prevalence was one in 10 or 9.9% (95%CI=7.5%-12.9%), which might be a more accurate prevalence. The T2DM prevalence rate observed in people with AUDs is similar to the T2DM prevalence observed in people with severe mental illness (11.3%, 95%CI=10.0% to 12.6%), which was double the relative risk for T2DM found in a matched background general population (Vancampfort et al., 2016). Rigorous meta-analytic data comparing the T2DM prevalence in people with AUDs versus age- and gender matched healthy controls are currently absent. However, in a recent large-scale ($n=21,616$) survey in a middle-age and elderly population, both women [odds ratio (OR)=1.32; 95% CI=1.05-1.65, $p<0.05$], and men (OR=1.84; 95% CI = 1.45-2.33, $p<0.01$) with past history of AUDs had an increased risk for diabetes than those without a history of AUDs (Udo et al., 2015). As the T2DM risk seems to be increased compared with general population data and the prevalence observed is comparable with those of people with severe mental illness, who are considered an important high risk group (Stubbs et al., 2015; Vancampfort et al., 2015a; Vancampfort et al., 2015b), investigating demographical, clinical and treatment-related factors that could influence T2DM frequency is needed.

Knowledge of factors associated with a high T2DM risk can also help identify individuals at greatest need for intensive monitoring and intervention. Due to lack of data we were not able to explore whether illness duration, smoking (%), physical inactivity (%), employment status (%)

employed), marital status (% single), % psychiatric co-morbidity (DSM or ICD), % physical co-morbidity (ICD) and treatment-related factors (% on psychotropic medication) moderated the pooled T2DM prevalence. As observed previously in people with severe mental illness (Vancampfort et al., 2015b) increasing age increases the risk for T2DM. In contrast to people with severe mental illness (Vancampfort et al., 2016), we however found that men with AUDs had a higher risk for developing T2DM than women. Several factors, including hormonal effects and less statistical power due to a lower number of women included, may have contributed to these gender differences. Future research should explore whether endogenous sex hormones which are reported to modulate glycemic status and risk of T2DM differentially in men and women could clarify the lower T2DM prevalence in women with AUDs (Ding et al., 2006). For example, cross-sectional and prospective studies found that sex-hormone-binding-globulin (SHBG) is more protective in women than in men ($P \leq 0.01$ for sex difference for both), with prospective studies indicating that women with higher SHBG levels (>60 vs ≤ 60 nmol/L) had an 80% lower risk of type 2 diabetes (RR, 0.20; 95% CI, 0.12 to 0.30), while men with higher SHBG levels (>28.3 vs ≤ 28.3 nmol/L) had a 52% lower risk (RR, 0.48; 95% CI, 0.33 to 0.69) (Ding et al., 2006). Previous research demonstrated that alcohol intake might lower SHBG levels (Thaler et al., 2015).

Finally, patient or physician self-report yielded numerically the highest T2DM prevalences followed by data based on OGTT assessment. The higher T2DM prevalence in self-report studies is likely due to the fact that in these studies patients were followed a longer period by the reporting physician extending the detection period. Unfortunately, due to lack of data we could not explore T2DM prevalence differences between cross-sectional and retrospective studies in order to confirm this hypothesis.

Clinical implications

Considering the high T2DM prevalence observed, screening for and trying to minimize risk factors should be key in the multidisciplinary treatment of people with AUDs. More specifically, people with AUDs should be considered as a clinical population that needs proactive screening for T2DM. It is particularly important to establish baseline T2DM risk at initial presentation so that any subsequent change during treatment can be monitored. The medical history and examination should, at a minimum, include: (a) history of previous cardiovascular diseases, T2DM or other related diseases, (b)

family history of premature cardiovascular diseases, T2DM or other related diseases, (c) smoking, dietary and physical activity habits, (d) weight and height in order to calculate body mass index (BMI), and waist circumference, (e) fasting blood glucose and/or hemoglobin A1c (HBA1c) if services and/or facilities are available, (f) blood pressure (measured twice and average taken), and (g) past medication history (De Hert et al., 2011). As there are differences in T2DM prevalences across T2DM assessment methods, it is recommended that ideally data based on oral glucose tolerance testing as the gold-standard are obtained. The frequency of glucose metabolism testing will depend on the patient's medical history, the prevalence of baseline risk factors and in less developed countries the facilities available. For those with normal baseline tests, it is recommended that measurements should be repeated at least annually with more frequent assessments in high risk patients, such as those with significant weight gain, post-partum diabetes or a first degree family history of diabetes. In patients with T2DM (and those with pre-diabetes), fasting blood glucose and HBA1c should be measured more frequently (approximately every 3–6 months) (De Hert et al., 2011). An annual examination should at a minimum include measurement of cardiovascular risk factors, an eye examination and foot examination to diagnose early signs of complications (De Hert et al., 2011).

Despite the imperative to screen for T2DM, screening for T2DM and cardiovascular risk factors is still suboptimal in mental health care settings with only slight improvement over the last decade (De Hert et al., 2011). The low glucose screening rates may reflect both patient and professional barriers. Professional barriers to screening within mental health settings may reflect a lack of clarity regarding clinical responsibility for the screening process, lack of understanding about what should be measured and when, uncertainty about how to interpret results, and lack of access to necessary equipment, as well as incomplete communication between primary and secondary care (De Hert et al., 2011). Without systematic screening using acceptable and accurate diagnostic tests, the true prevalence of T2DM in patients with AUDs will remain unknown. Even after an established diagnosis of T2DM is made, many people with AUDs are not offered timely treatment. Thus, routine screening is only the first step. Psychiatric centers should cooperate with diabetes experts to establish shared care pathways and ensure an integrated approach for people with AUD and T2DM.

Limitations

Whilst this is the most comprehensive meta-analysis of T2DM in people with AUDs conducted to date, we acknowledge several limitations that are largely reflected by factors in the primary data. First, a threat to the validity of any meta-analysis is publication bias and heterogeneity, which we encountered in most of our analyses. Nevertheless, we adjusted for publication bias using the trim and fill analysis and were able to explain over half of the between study heterogeneity in our multivariable meta-regression analysis. Second, there were inadequate data on lifestyle behaviors, concomitant somatic and psychotropic medication use, smoking rates, physical inactivity, marital and employment status precluding meta-analytic assessment of these factors as moderating or mediating variables. Third, rigorous data comparing the risk for T2DM in people with AUDs with age- and gender-matched healthy controls in large-scale studies are currently missing. Despite the abovementioned caveats, this is the largest study of T2DM risk in people with AUD and the first meta-analysis pooling all available data.

Future research

First, the pathophysiology underlying the association between AUDs and T2DM is complex and not well understood, requiring further investigation. Previous studies exploring the associations between alcohol use and cardiovascular risk factors (Fernández-Solà, 2015) including T2DM (Conigrave and Rimm, 2003), have resulted in inconsistent associations. This could be due to the fact that the dose–response relationship between alcohol and metabolic health has been reported to follow a J- or U-shaped curve, pointing to lower all-cause mortality among light to moderate drinkers compared to heavy drinkers (Fernández-Solà, 2015). Any potentially beneficial effect is apparent only at low to modest use (Mostofsky et al., 2016). However, this epidemiological evidence has also been criticized due to misclassification and confounding (Chikritzhs et al., 2015). Using Mendelian randomisation analysis of 56 epidemiological studies (n=261,991), it was reported recently that reductions in alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health (Holmes et al., 2014; Stockwell et al., 2016). In order to better understand the T2DM risk in people with AUD more cross-sectional and in particular longitudinal studies are needed to compare the risk with well-matched healthy controls. Second, future research should comprehensively assess T2DM risk factors following, at the very least, recommended monitoring guidelines and evaluate the optimal monitoring regimen

and interventions. Third, long-term follow-up is required to accurately document the emergence of more distal outcomes, such as ischemic heart disease, medical costs, and premature mortality (52).

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Conflict of interest

Dr. Vancampfort is funded by the Research Foundation – Flanders (FWO-Vlaanderen). Dr. De Hert report being a paid consultant for, receiving grant or research support and honoraria from, and serving on the speakers' bureaus or advisory boards of Janssen-Cilag, Lundbeck, and Takeda. The other authors declare that they have no conflicts of interest to report.

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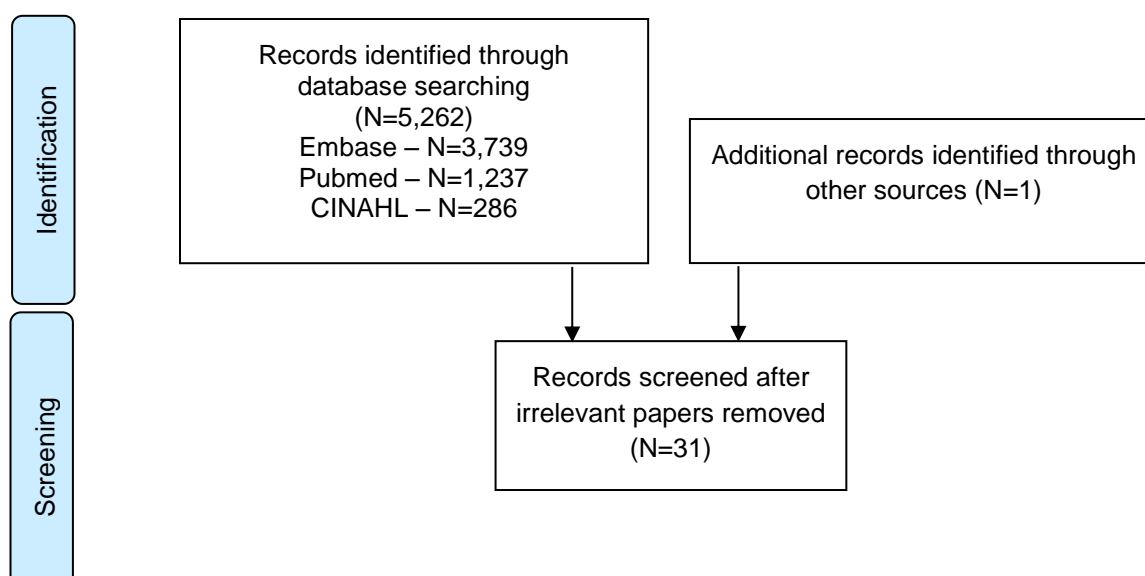
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Figure 1. PRISMA flow diagram



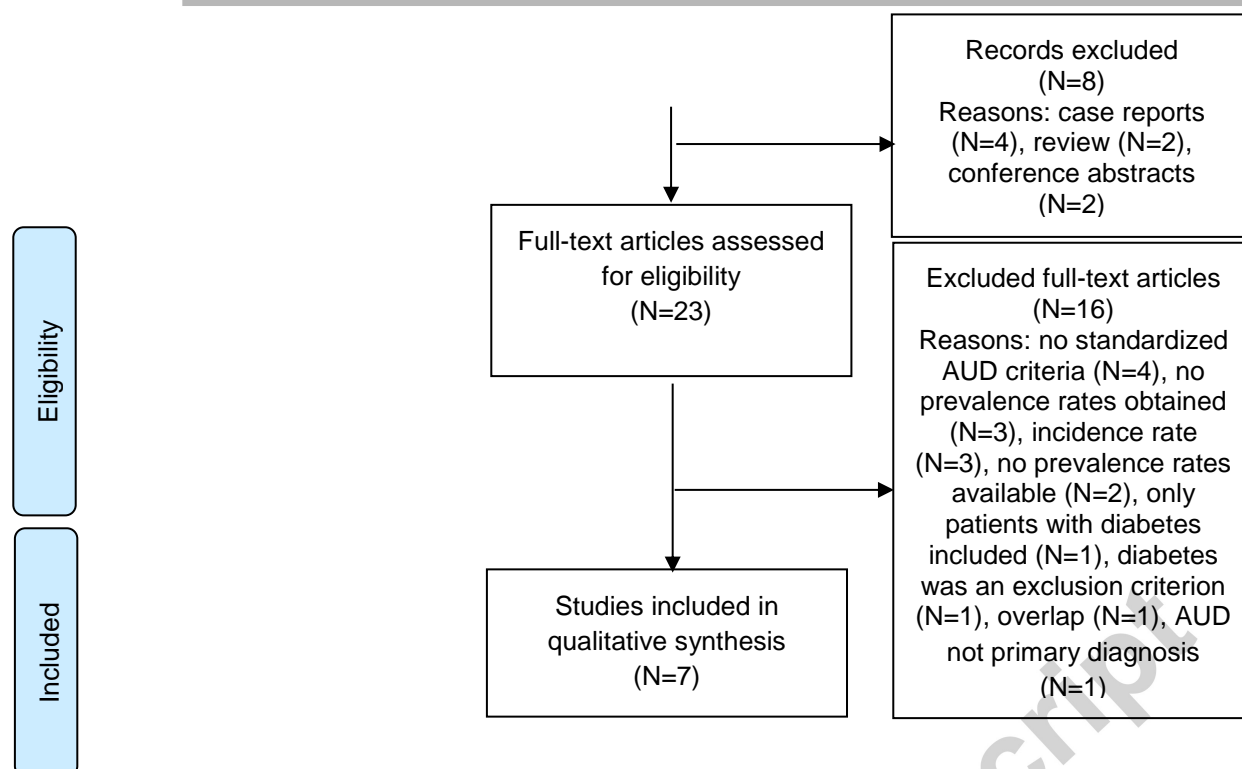


Table 1. Details of the included studies

| First Author (year) | Country | Participants | T2DM assessment | T2DM prevalence | T2DM prevalence Controls* |
|---------------------|----------------|--|--|-----------------|---------------------------|
| David 2004 | USA | 38 male Veterans with DSM-IV alcohol dependence; 48.3±8.0 years; 18% employed; 55% major depressive disorder; 26.6±9.0 alcohol abuse-years | fasting glucose | 8.0% | / |
| Ju 2011 | South-Korea | 118 male inpatients with DSM-IV alcohol dependence; 49.1±0.9 years; 11.4 years problematic drinking | OGTT | 22.0% | / |
| Chandini 2013 | India | 100 inpatients with ICD-10 alcohol dependence; 88% employed; 65% physical co-morbidity | physician report based on laboratory screening | 23.0% | / |
| Glaus 2013 | Switzerland | 264 (42♀) community patients with DSM-IV alcohol abuse; 50.1±8.7 years | fasting glucose | 10.2% | / |
| | | 173 (46♀) community patients with DSM-IV alcohol dependence; 51.1±8.2 years | fasting glucose | 9.2% | / |
| Pach 2014 | Czech Republic | 88 male inpatients with ICD-10 alcohol dependence; 39.2±7.8 years; illness duration=10.6 ±7.8years | OGTT | 10.2% | / |
| Hong 2015 | South-Korea | 1,318 male community participants with AUDIT-score≥15; 45.1±0.4 years; 50.1% physical co-morbidity; 48.7% physically inactive; 77.3% smoking | fasting glucose | 11.2% | / |
| | | 239 female community participants | fasting | 3.5% | / |

| | | | | | |
|-------------|----------------------|--|------------------|-------|---|
| | | with AUDIT-score \geq 15; 45.1 \pm 0.4 years; 51.5% physical co-morbidity; 54.5% physically inactive; 11.6% smoking | glucose | | |
| Odlaug 2015 | Europe (8 countries) | 1660 (523 \varnothing) participants in mixed settings; 48.3 \pm 12.6 years; 26.5% single status; 43.1% major depressive disorder; 64% psychiatric co-morbidity; 50% physical co-morbidity | physician report | 13.2% | / |

OGTT= Oral Glucose Tolerance Test; AUDIT= Alcohol Use Disorders Identification Test

Table 2. Subgroup analyses of moderators of type 2 diabetes in people with alcohol use disorders

| Analysis | Meta-analysis | | | | I ² |
|-----------------------------------|-----------------------|-------------|-------------|----------------------------------|----------------|
| | Number of comparisons | Effect size | 95% CI | Between group difference p-value | |
| Population based or not | | | | 0.015 | 80.0 |
| Population based | 4 | 9.9% | 7.5%-12.9% | | |
| Non-population based | 5 | 17.2% | 12.0%-24.0% | | |
| Study setting | | | | 0.27 | 80.0 |
| Mixed settings | 1 | 13.2% | 5.4%-28.9% | | |
| Inpatient settings | 4 | 16.1% | 9.6%-25.8% | | |
| Outpatient settings | 2 | 9.9% | 4.9%-19.1% | | |
| Community settings | 2 | 7.0% | 3.4%-13.9% | | |
| Diabetes assessment method | | | | 0.05 | 80.0 |
| Fasting glucose | 5 | 18.5% | 5.7%-12.4% | | |
| Oral glucose tolerance test | 2 | 16.1% | 9.0%-27.3% | | |
| Self- or physician report | 2 | 16.9% | 10.2%-26.7% | | |
| Geographical region | | | | 0.73 | 80.0 |
| North-America | 1 | 7.9% | 1.9%-27.6% | | |
| Europe | 4 | 10.9% | 6.8%-16.9% | | |
| Asia | 4 | 12.9% | 8.2%-19.9% | | |

Table 3. Meta-regressions of moderators of type 2 diabetes in people with alcohol use disorders

| Moderator | Number of comparisons | β | 95% CI | p-value | R ² |
|---------------------------|-----------------------|---------|---------------|---------|----------------|
| Mean age (years) | 8 | 0.07 | 0.01 to 0.12 | 0.015 | 0.60 |
| Gender (% male) | 9 | 1.34 | 0.44 to 2.24 | 0.003 | 0.66 |
| Physical co-morbidity (%) | 4 | 6.8 | -1.39 to 15.0 | 0.104 | 0.49 |

Highlights

- Approximately one in 8 individuals with alcohol use disorders has diabetes.
- Older age and male gender are risk factors for diabetes in alcohol use disorders.
- People with alcohol use disorders have a comparable diabetes risk than those with severe mental illness.
- Routine screening for diabetes is needed in those with alcohol use disorders.